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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,994	05/03/2001	Kristiina Ylihonko	1574/49884	7174

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EXAMINER	
KERR, KATHLEEN M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,994	YLIHONKO ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 9-15* is/are pending in the application.

4a) Of the above claim(s) *4 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/14/01, 5/3/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (mailed on October 24, 2003), Applicants filed an election received on November 26, 2003. Claims 1-5 and 9-15 are pending in the instant Office action.

Election

2. Applicants' election with traverse of Group I, Claims 1-3 and 9-15, in a paper received on November 26, 2003 is acknowledged. The traversal is on the ground(s) that since the individual genes of the cluster are a part of the entire cluster, a search for the entire cluster will necessarily include a search of all its parts. This is not found persuasive because all the portions of the cluster must be taught in the art to anticipate the claims. Thus, if a search of a portion of the cluster is found free of the art, then the entire cluster must be free of the art. Therefore, all the genes of the cluster need not be searched to search the cluster as a whole.

Applicants further argue that the Examiner has misinterpreted the invention; the Examiner assures Applicants that that is not the case. The Examiner fully understands the utility of the claimed inventions, including individual pieces, in the biosynthesis of analogs of anthracyclines using particular intermediates that may be easy to chemically synthesize. It certainly follows that the individual pieces are useful in their own right as will as in the combination with the entire set of genes for this reason. The Examiner also fully comprehends the concept that aclacinomycins are a group of compounds and not a single compound. The Examiner does not disagree that the primary function of the separate genes may be to act as a group and produce aclacinomycins; however, their individual functions that are useful

independent of producing the final product render them distinct inventions as previously set forth.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. The instant application is granted the benefit of priority for the International Application No. PCT/FI00/00819 filed on September 25, 2000 as the national stage entry. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

The instant application also requests benefit of the foreign application 19992085 filed on September 29, 1999. A copy of this document, in English, *absent the claims*, is in the file from the international application process; said copy demonstrates the teaching of the claimed sequence to this earliest claimed date of September 29, 1999; however, support for the 84% homology breadth in Claims 2-3 and 9-15 is not found. If support is in the Finland-filed claims, a copy of the claims from the official priority document should be provided by Applicants if available. The recitation of 84% homology is not found anywhere else in the Finland application.

Information Disclosure Statement

4. The information disclosure statements filed on May 3, 2001 and August 14, 2001 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Objections to the Specification

5. The specification is objected to for lacking clarity in its examples. On pages 9-10, the cloning of the gene cluster is presented. On page 10, primers are described as being related to the *galilaeus* dehydratase gene; these are SEQ ID NOs: 15 and 16. How these primers were formulated is not described. This step is key to understanding the cloning process (i.e., what similar gene from a different organism was used to hybridize to the *galilaeus* gene cluster). Clarification is required. If this information is in the specification elsewhere, it should be amended into this experimental section noted. If not, this information should be made of record but not amended into the specification, as it would constitute new matter.

Objections to the Claims

6. Claims 2-3 and 9-15 are objected to for being drawn to non-elected subject matter. All references to portions or parts of the full gene cluster must be removed from the claims and will not be considered within the scope of the claims for the purposes of examination herein. In Claims 2 and 3, this means deletion of "or part thereof having similar characteristics".

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3, and 9-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "anthracycline biosynthetic pathway" is unclear as

to its metes and bounds. Biosynthetic pathways are extensive and complicated as to just which genes are encompassed, particular in early stages of intermediate production. Either all the intermediates or all the genes/enzymes must be defined to clearly define a biosynthetic pathway.

The specification focuses on genes in Figure 2; some (not all) of these genes are assigned enzymatic steps on the pathway in Figure 3 converting a phospho-sugar into 2-deoxyfucose, rhodosamine, and rhodinose. These three sugars are combined with aklavinone (a 4-ringed structure) to produce aclacinomycins. Thus, this gene cluster, while being a portion of a gene cluster for the production of anthracyclines, actually appears to be only a gene cluster to produce 2-deoxyfucose, rhodosamine, rhodinose, and perhaps other sugars. In other words, SEQ ID NO:14 does not encompass "**the** gene cluster for **the** anthracycline biosynthetic pathway" (emphasis added). Clarification as to the functionality of the disclosed gene cluster is required; said clarification should extend into the claim language since one of skill in the art would interpret the phrase "the gene cluster for the anthracycline biosynthetic pathway" to encompass all the genes necessary to make anthracyclines.

8. Claims 2, 3, and 9-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "84% homology" is unclear; no support in the specification can be found, except in the claims. Is this meant to be 84% identity over the full-length of SEQ ID NO:14? In the art, homology can apply to highly homologous portions of sequences. Thus, the metes and bounds of the term are unclear. Clarification is required.

9. Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "**the** DNA fragment of claim 2" (emphasis added) is confusing and improper since Claim 2 encompasses more than a single fragment; it is drawn to a genus. The appropriate article is ---a--- or ---said---. Alternatively, the term "**the** plasmid replicating in *Streptomyces* or in *E. coli*" (emphasis added) indicates one particular plasmid while no single, particular plasmid is indicated in the claims or the specification. Thus, the metes and bounds of this phrase are also unclear; the Examiner suggests ---a plasmid---.

10. Claims 12, 13, and 15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "metabolites" or "anthracycline metabolites" are totally unclear as to their metes and bounds. In Claim 12, can this mean any compound? In Claim 13, what is the smallest component, and to what degree of degradation, is a metabolite of anthracycline still considered a metabolite? Clarification is required.

11. Claims 14 and 15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "activator" and "polyketide assembler" are unclear. For the former, an activator or what? For the later, the term is unknown in the polyketide synthase field to the Examiner and not explanation is supplied in the specification. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1 and 9-15 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 is drawn to a DNA fragment that is claimed solely by function and without any definite structural limitations.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, a DNA fragment that is a portion of a gene cluster for the anthracycline biosynthetic pathway is disclosed as SEQ ID NO:14. Said fragment can be found

in the genome as a 7kb XhoI-NotI fragment overlapping with an 8.5 kb BglII-BglII fragment from the *S. galilaeus* genome (see Figure 2). This limited structure of the gene cluster portion, namely size and restriction map, in no way correlates to the function required, only the structure that is SEQ ID NO:14 can do that. Without specific structure, the claim is drawn to any gene cluster for anthracycline biosynthesis that happens to be contained in fragments of the noted size and restriction map. Thus, the claims are drawn to a genus of DNA fragments, and one of skill in the art would be unable to predict the structure of other members of this genus by virtue of the instant disclosure.

13. Claims 2, 3, and 9-15 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 2 is drawn to DNA fragments with at least 84% homology to SEQ ID NO:14.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the

common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses a DNA fragment encoding polypeptides necessary to produce aclacinomycins in a heterologous host cell; this DNA fragment of SEQ ID NO:14. Applicants have fully described the genus relating to said SEQ ID NOs with both sequence identity limitations and functional limitations. However, the genus of the instant claims also contains DNA fragments within the sequence identity limitations, but having different function. Applicants have not fully described a genus that has sequence identity limitations in the absence of functional limitations.

14. Claims 2, 3, and 9-15 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for the DNA fragment that is SEQ ID NO:14, does not reasonably provide enablement for polynucleotides with such low sequence homology, such as the 84% claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The amount of experimentation required of one of skill in the art to use the claimed invention to the full extent of its scope is undue.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404).

Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

Applicants present no guidance or working examples of the use of polynucleotides that have such low sequence identity with respect to SEQ ID NO:14. The nature of the invention is such that the DNA encodes functional proteins, those useful in the biosynthetic pathway of aclacinomycins; and with such a great deviation from the known sequence, the predictability of functionality becomes extremely low. While the instant specification describes and enables means for identifying other anthracycline biosynthetic pathway genes using hybridization methods, etc., these methods do not enable one of skill in the art to make all, or a relevant portion of, the polynucleotides within the scope of the claims because the ability to find an anthracycline biosynthetic pathway gene, which is structurally related to SEQ ID NO:14, is not equivalent to the ability to make an anthracycline biosynthetic pathway gene as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the disclosed sequence so that its anthracycline-

biosynthetic-pathway -nature is maintained. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

15. Claims 9, 11, 12, and 14 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods of increasing aclacinomycin production and/or producing metabolites in a *Streptomyces* host that naturally produces aclacinomycins, does not reasonably provide enablement for methods of increasing or producing in all *Streptomyces* hosts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The amount of experimentation required of one of skill in the art to use the claimed invention to the full extent of its scope is undue.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant specification teaches a gene cluster containing 13 genes described as encoding enzymes involved in aclacinomycin biosynthesis; most activities of these encoded proteins are "deduced" according to homologous sequence in databases (although these homologous sequences are not disclosed) (see Table 1 on page 12 of the specification). Only 9 genes, those encompassed by Sg4, are used in complementation assays to assign functionality putatively. Only Sg4 is transformed into *S. peuceticus* and *S. galilaeus* to increase aclacinomycin production. Thus, no description of using the entire gene cluster in any *Streptomyces* host cell to make aclacinomycins is taught. Moreover, from the figures, it is clear that SEQ ID NO:14 does not comprise all the genes necessary to make a complete anthracycline;

said genes participate in the production of the sugars attached to the aklavinone structure. One of skill in the art would be unable to predict if SEQ ID NO:14 contains the entire gene cluster capable of producing aclacinomycins in a heterologous host (that is, one that does not produce aclacinomycin naturally). Thus, one of skill in the art would be unable to practice the claimed methods in all *Streptomyces* host cells. Claim 11 is included in the instant rejection because no limitation of the derivation from *S. galilaeus* is in the claim, thus, the mutant used could be one that does not natively produce aclacinomycins.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claims 2, 3, and 9-15 are rejected under 35 U.S.C. § 102(a) as being anticipated by Raty *et al*. (see IDS). For the record, the Examiner notes that the date of public availability is July 13, 2000, which is the date the document was published online (see page 164 of document) and not September 2000 as noted in the IDS. The instant claims are drawn to DNA of SEQ ID NO:14 in a plasmid that replicates in *Streptomyces*; the instant claims are also drawn to methods of using said DNA in an *S. galilaeus* mutant, like H039, or *S. peuceticus* to produce aclacinomycins and/or metabolites thereof.

Raty *et al*. teach the 14807 bp DNA of SEQ ID NO:14 as well as using said DNA in a plasmid to produce anthracyclines in H039 and *S. peuceticus* (see Figure 2 and page 166, right column).

The Examiner notes that the instant claims have been afforded priority only to the PCT filing date (not the foreign priority date) based on a lack of support for the 84% homology limitation as noted above.

Conclusion

17. Claims 1-3 and 9-15 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

February 6, 2004